UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/320,767	05/27/1999	NICK GIANNOUKAKIS	A32362	5337

21003 7590 04/06/2004

BAKER & BOTTS
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/320,767	GIANNOUKAKIS ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Action is in response to the communication filed on 1/20/04. The amendment has been entered. Claims 1-30 have been cancelled, as instructed. New claims 31-42 have been added. Claims 31-42 and are currently pending in the application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Drawings

The objection to the drawings has been withdrawn in view of the new drawings, submitted 6/24/03, which are deemed acceptable for examination purposes.

Specification

3. The disclosure is objected to because of the following informalities: it appears that the specification (and some claims as indicated below) contains typographical errors. Specifically, the specification includes "NF-Kβ" (e.g., see page, line 5); however, "NF-Kβ" appears to be a typographical error because "NF-κB" (i.e., "NF-kappa-B", not "NF-K-beta") is the only similar recognized molecule in the prior art. It is noted that the specification does indicate the proper molecule, "NF-κB"(on page 17, line 1, for instance). Therefore, it appears that "NF-Kβ" is merely a typographical error and appropriate correction is required.

Miscellaneous

Claims 31-38 encompass methods for reducing beta-cell dysfunction or FADD mediated beta-cell apoptosis wherein beta-cells are transformed with a nucleic acid that expresses an inhibitor of IL-1beta or FADD mediated apoptosis, respectively, and then transplanting said beta cells into the individual. It is noted that the claims rejected in the previous Office Action (mailed 12/18/02) did not encompass transplanting the beta cells into an individual (as indicated in the previous Office Action). As such, the instant claims encompass new limitations which necessitate the new grounds of rejection se forth herein. Since the new grounds of rejection necessitate the new rejections (which are similar to the previous rejections), the Office Action is made final.

Claim Objections

4. Claims 33 and 41 are objected to because of the following informalities: it appears that the instant claims contain typographical errors. Specifically, the claims include "NF-Kβ"; however, "NF-Kβ" appears to be a typographical error because "NF-κB" (i.e., "NF-kappa-B", not "NF-K-beta") is the only similar recognized molecule in the prior art. It is noted that the specification does indicate the proper molecule, "NF-κB"(on page 17, line 1, for instance). Therefore, it appears that "NF-Kβ" is merely a typographical error and appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 39-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 recites the limitation "said β cell dysfunction" in 3. There is insufficient antecedent basis for this limitation in the claim. Claims 40-42 depend on claim 39 and are, therefore, rejected for the same reason.

Claim Rejections - 35 USC § 112, first paragraph

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 31-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record, and in addition for the reasons set forth below.

The instant claims are drawn to methods for 1) reducing beta-cell dysfunction in an individual with diabetes, by introducing a nucleic acid encoding an inhibitor of IL-1beta into a beta cell and transplanting the beta cell into the individual (claims 31-34) and 2) reducing Fas

mediated beta-cell apoptosis in an individual with diabetes, by introducing a nucleic acid encoding an inhibitor of Fas mediated apoptosis into a beta cell and transplanting the beta cell into the individual (claims 35-38); as well as a mammalian beta-cell comprising a recombinant nucleic acid molecule, said nucleic acid molecule comprising and expressing an inhibitor of IL-1 beta activity (claims 39-42).

All of the claims encompass nucleic acid molecules that encode an inhibitor of IL-1 beta (or Fas mediated apoptosis)—with the generic claims encompassing an IL-1 beta inhibitor or an inhibitor of Fas mediated apoptosis (e.g., see claims 31, 35 and 39), and dependent claims narrowing the inhibitors to an interleukin-1 receptor antagonist protein (claims 32 and 40), an NF-kβ inhibitor (claims 33 and 41), an insulin like growth factor-1 (claims 34 and 42), an dominant negative mutant of the Fas protein (claim 36), a dominant negative mutant of the FADD protein (claim 37), a member of the bcl-2 protein family (claim 38). It is noted that the claims, as written, do not explicitly limit the instant claims to any particular molecule, such as a specific IL-1 beta inhibitor or a specific inhibitor of Fas mediated beta-cell apoptosis. As such, the claims encompass any IL-1 beta inhibitor and any inhibitor of Fas mediated beta-cell apoptosis—as well as any interleukin-1 receptor antagonist protein, any NF-kβ inhibitor, any insulin like growth factor-1, any dominant negative mutant of the Fas protein, any dominant negative mutant of the FADD protein, and any member of the bcl-2 protein family. Considering the breadth of the claims, the claims encompass several genuses of inhibitors wherein each genus is indeterminate in size, but may encompass thousands if not millions of different molecules, considering all of the possible inhibitors, including those inhibitors that have yet to be identified,

including inhibitors that may have completely unrelated structures and that may utilize completely different functional pathways, compared to any known inhibitors.

The written description guidelines indicate that the description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, by disclosure of relevant identifying characteristics (i.e. structure or other physical and/or other chemical properties), by disclosure of functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164). Regarding the description of a representative number of species, the guidelines note "a satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the **necessary common attributes or features of the elements possessed by the members of the genus** in view of the species disclosed." (Emphasis added; see: Federal Register: December 21, 1999, Volume 64, Number 244; revised guidelines for written description). In the instant case, no common attributes or features possessed by the inhibitors are disclosed. There is no indication of any relevant common structural/chemical characteristics, and no identification of any structural limitations/requirements which provide guidance on the identification of molecules that meet the functional limitations.

With respect to the disclosure in the specification of a method for identifying any species encompassed by the claims, it is noted that MPEP 2163 indicates,

> "The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic,

without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

The method disclosed to identify any inhibitor merely identifies the claimed molecules by function. There is no indication in the specification or the prior art teaching the relationship between the structure of the inhibitors and their function.

With respect to the inhibitors encompasses by the dependent claims, it is noted that the claims do not limit the inhibitors to any particular inhibitor, nor are the claims limited to a class of inhibitors that share common structural features or that have similar functions. For instance, the inhibitors encompassed by the claims drawn to an inhibitor that is an interleukin-1 receptor antagonist protein include decoy receptors, ligands that bind the receptor and act as competitive inhibitors, intracellular dominant negative proteins, etc. Inhibitors encompassed by the claims drawn to an inhibitor that is an NF-kβ inhibitor include proteins such as dominant negative proteins, antibodies that bind to and inhibit NF-kβ as well as antisense nucleic acids which inhibit the expression of NF-kβ, etc. Inhibitors encompassed by the claims drawn to an inhibitor that is an insulin like growth factor-1 (IGF-1) include IGF-1, as well as any variants of IGF-1 that have IGF-1 function. Inhibitors encompassed by the claims drawn to an inhibitor that is a dominant negative mutant of the Fas protein, include all Fas mutants that act as dominant negative proteins. Inhibitors encompassed by the claims drawn to an inhibitor that is a dominant negative mutant of the FADD protein, include all FADD mutants that act as dominant negative proteins. However, the specification and supporting material have not described a representative number of dominant negative Fas or FADD proteins, considering the large number of molecules encompassed by these claims. Inhibitors encompassed by the claims drawn to an inhibitor that is

a member of the bcl-2 protein family, include all members of the bcl-2 family, some of which are known to be pro-apoptotic molecules and some of which are known to be anti-apoptotic molecules. The specification and related material does not indicate the structural characteristics common to the bcl-1 family members—there is no indication of common attributes common to all pro-apoptotic or to all anti-apoptotic molecules. As such, the specification has not adequately described a representative number of the broad class of IL-1 beta inhibitors (such as those encompassed by claims 31, 35 and 39), nor has the specification adequately described a representative number of any f the narrower classes of IL-1 beta inhibitors (such as those encompassed by claims 32-34, 36-38 and 40-42).

3. Additionally, Claims 31-42 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

4. As mentioned above, the claims encompass inhibitors for which are not adequately described in the specification considering the broad genus of molecules encompassed by the claims. Without an adequate description of a representative number of inhibitors encompassed by the claims, one of skill in the art would not know how to make or use the claimed invention without performing an undue amount of additional experimentation.

5. In addition to the rejection(s) above, claims 31-42 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a method of reducing beta-

cell apoptosis in an individual that has diabetes, said method comprising transfecting an isolated beta-cell of said individual with a nucleic acid molecule encoding IRAP or IGF-1 and transplanting the transfected beta-cell into the pancreas of said individual, wherein expression of said nucleic acid molecule in said transplanted beta-cell results in reduction of apoptosis in said transplanted beta-cell compared to a control beta-cell (claims 31-34); a method of reducing Fas-mediated beta-cell apoptosis in an individual having diabetes, said method comprising transfecting an isolated beta-cell of said individual with a nucleic acid molecule encoding IRAP or IGF-1 and transplanting the transfected beta-cell into the pancreas of said individual, wherein expression of said nucleic acid molecule in said transplanted beta-cell results in reduction of apoptosis in said transplanted beta-cell compared to a control beta-cell (claims 35-38); and a mammalian beta-cell comprising a recombinant nucleic acid molecule, wherein said nucleic acid molecule encodes and expresses IRAP or IGF-1, wherein the expression of said IRAP or IGF-1 reduces apoptosis in said mammalian beta-cell compared to a control cell, does not reasonably provide enablement for the full scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The instant claims are drawn to a method of reducing beta-cell dysfunction (including Fas-mediated beta-cell apoptosis) that results in diabetes, comprising introducing a nucleic acid molecule encoding an inhibitor of IL-1beta into said beta cell, whereby expression of said nucleic acid molecule results in reduction of beta-cell dysfunction. Additionally, claims 39-42 are drawn to a mammalian beta-cell comprising a nucleic acid expressing an inhibitor of IL-1beta activity, wherein the beta-cell may be either in vitro or in vivo.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Nature of the Invention:

The claims are drawn to methods utilizing a transformed beta-cell as well as a transformed beta-cell comprising a vector which expresses an inhibitor of IL-1beta activity. The methods encompass treatment of beta-cell dysfunction that results in diabetes, and, as such, the claims encompass treatment of diabetes using the transformed cells. The only use contemplated in the specification for the claimed methods, and the claims mammalian beta-cell expressing an inhibitor of IL-1beta activity, is for the treatment of diabetes. Therefore, the nature of the invention is ex vivo gene therapy for the treatment of diabetes.

Breadth of the Claims:

The independent claims are very broad and encompass the treatment of a beta-cell dysfunction (or Fas-mediated beta-cell apoptosis) that results in diabetes by transplanting a beta-cell transformed with a vector that comprises and expresses an inhibitor of IL-1beta (or Fas mediated apoptosis), into an individual with a pancreatic disorder. Examples of beta-cell dysfunctions that result in diabetes include Type I diabetes or Type II diabetes (including all

symptoms associated with these types of diabetes including apoptosis, insulin production, insulin secretion, and insulin resistance).

The state of the prior art and unpredictability of the art:

As mentioned above, the claims are very broad and encompass ex vivo gene therapy treatment for diabetes, by administering a beta-cell comprising a nucleic acid that comprises and expresses an inhibitor of IL-1beta (or Fas mediated apoptosis).

Regarding gene therapy as a whole, the art at the time of filing considered gene therapy to be unpredictable as modes of delivery that would provide efficient expression of genes encoding the therapeutic polypeptide sufficient to provide an alleviation of symptoms related to the target disease or condition had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Anderson (Nature 392:25-30; 1998) teaches, "Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease... the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how in vivo immune defenses can be overcome and how to manufacture efficiently the vectors we do make."

Specifically regarding gene therapy for diabetes, Levine (Mol. Med. Today 5:165-171; 1999) indicates many of the obstacles that need to be overcome in order to create an effective gene therapy for diabetes including gene transfer problems, cell transfer problems, and the responsiveness of the transduced beta-cells to blood glucose levels.

Regarding gene transfer into beta cells, Levine indicates that there are two general means by which therapeutic genes can be introduced into beta cells: by transducing the islet cells ex vivo and reintroducing the cells in vivo (see p. 165, last paragraph), and transfer of the therapeutic gene(s) into beta-cells in vivo. However, Levine also indicates, "Successful islet cell transplantation has proved to be an elusive goal... (and) to date, there are no studies demonstrating that [in vivo gene transfer into beta-cells] can be done." (See p. 166). Furthermore, transplanting non-autologous beta-cells into the patient would not be expected to work, as the patients immune system would most likely attack the transplanted foreign cells, thus negating any possible positive effects they could have on the patient.

Levine teaches that both type I and type II diabetes results in the apoptotic death of beta-cells (see p. 166-167) and further indicates that preventing beta-cell apoptosis may be potentially applicable to both type I and type II diabetes (see p. 168, first column) either by inhibiting apoptosis of beta cells before they die by transfer of anti-apoptotic genes such as Bcl-2 into the beta cells, by regenerating beta cells, or by transplanting new/replacement cells for the beta cells (see p. 168-169). However Levine explicitly teaches that these methods **can not be predictably reproduced for several reasons** including: the transfer in vivo delivery of the therapeutic nucleic acid to the specific target cells (see Anderson as mentioned above), regeneration does not continue over long periods of time (see Liu p. 168, third column), and transplantation of cadaveric human islet cells has been disappointing in terms of achieving insulin independence largely because of the inability to obtain large quantities of the cells (see Liu, p. 168, column 2).

Levine also indicates that successful gene transfer into beta cells (either in vivo or ex vivo) and/or successful cell transplant are not the only obstacles to obstacle to overcome in order

to effectively treat diabetes. Once the therapeutic gene(s) or cells are successfully delivered, the cells must be able to respond changes in blood glucose levels:

> "A definitive treatment for diabetes mellitus will be one that maintains a normal blood glucose concentration in the face of fluctuating dietary intake. To accomplish this there must be mechanisms to sense the amount of blood glucose coupled to rapid release of the right amount of insulin." (See p. 165, abstract).

Therefore, any successful therapy for diabetes must allow the insulin producing cells to be responsive to the fluctuations of blood glucose levels, a demonstration not present in the instant specification.

Levine summarizes the state of gene therapy for diabetes by stating, "the ultimate goal of a definitive, permanent treatment of diabetes through gene therapy lies in the distant future." (p. 170, last paragraph).

Working Examples and Guidance provided:

The working examples and guidance provided in the specification (and declaration, see below) were indicated fully in a previous Office Action, and are summarized here. The only working examples presented encompass expressing an inhibitor of IL-1beta (specifically, either IL-1Ra/IRAP or IGF-1) in a mouse beta cell in vitro, followed by the transplantation of the beta cell into a mouse model for Type I diabetes. The results present only indicate that the transplanted beta cells had a reduced incidence of apoptosis compared to control cells (see declaration). There is no evidence presented indicating that the methods used resulted in a definitive, permanent treatment of diabetes.

Quantity of Experimentation:

Considering the number of obstacles recognized in the art which must be overcome for successful gene therapy treatment for diabetes, and considering that the only examples presented

as evidence indicate only that the transplantation of beta-cells which express exogenous IL-1Ra/IRAP or IGF-1 results in a reduction in the incidence of beta-cell apoptosis. There is no indication that the methods or cells result in the transformed beta-cells are sensitive and responsive to fluctuating blood glucose levels—a requirement for definitive, permanent treatment of diabetes. Therefore, more experimentation is required in order to overcome the remaining obstacles for the treatment of beta-cell dysfunction that results in diabetes.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy for diabetes recognized in the art, the breadth of the claims, the limited amount of working examples and guidance provided, and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 39 is rejected under 35 U.S.C. 102(b) as being anticipated by Liu et al. (Human Gene Therapy 7:1719-1726; 1996).

Claim 39 is drawn to a mammalian beta-cell comprising a recombinant nucleic acid molecule that comprises and expresses an inhibitor of IL-1 beta activity. It is noted that the claim indicates that the expression of the inhibitor reduces "said beta cell dysfunction". However, there is no antecedent basis for "said beta cell dysfunction", as such, the claim is interpreted only as a mammalian beta-cell comprising a recombinant nucleic acid molecule that comprises and expresses an inhibitor of IL-1 beta activity. It is also pointed out that the specification indicates that Bcl-2 is an inhibitor of IL-1 beta activity (e.g., see page 18 of the specification)

It is noted that the claims are very broad and encompass both in vitro as well as in vivo embodiments. The instant rejection is only directed to in vitro embodiments; specifically, the embodiments wherein the nucleic acid is delivered to an isolated (i.e. in vitro) mammalian beta-cell.

Liu teaches a mammalian cell (specifically, a human or mouse beta-cell) comprising a vector which comprises and expresses Bcl-2 (see p. 1724, Figure 4A). Liu also teaches that administering said vector to said beta-cells inhibits cytokine-induced apoptosis in said beta-cells (e.g., see p. 1724, Figures 4 and 5). Therefore, Liu clearly anticipates claims 39.

Response to Arguments

8. Applicant's arguments filed 6/24/03 have been fully considered but they are not persuasive.

Applicants indicate that the claims have been amended to indicate that that the beta-cell dysfunction results in diabetes, and thus should overcome the rejections as they pertain to treating "any beta-cell dysfunction" (see p. 5 of the reply).

In response, it is acknowledged that the claims have been amended as indicated, however, the claims are still very broad, and encompass treating diabetes using ex vivo gene therapy, as indicated herein. As such, although the claims are no longer drawn to any beta-cell dysfunction, the claims are still not enabled to the full scope encompassed by the claims for the reasons set forth herein.

Applicants also argue that the present invention relates to methods of reducing beta-cell dysfunction, and that the invention is not related to, nor do the claims encompass novel inhibitors of IL-1beta (see p. 5). Applicants also point out that they have two specific examples of IL-1 beta inhibitors (IRAP and IGF-1); and also indicate that they have indicated methods for determining if a molecule is an IL-1beta inhibitor (see p. 6)

In response, it is respectfully pointed out that the claims are not limited to any specific IL-1 beta inhibitors, but rather encompass different genuses of molecules, wherein each genus of molecules can encompass molecules that have not been adequately described and which also encompass molecules that have yet to be identified (see above). Furthermore, the two specific inhibitors identified (IRAP and IGF-1) are not considered a representative number of the huge number of IL-1beta inhibitors encompassed by the claims. With respect to applicants' arguments that they have disclosed methods for determining if a molecule is an IL-1beta inhibitor, it is respectfully pointed out that MPEP 2163 states,

> "The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

The method disclosed to identify any IL-1beta inhibitor merely identifies the claimed molecules by function. There is no indication in the specification or the prior art teaching the relationship between the structure of the inhibitors and their function. As such, Applicants arguments are not persuasive.

Applicants arguments as they pertain to rejections under 35 USC 112, second paragraph and 35 USC 103 are moot in view of the cancellation of claims and submission of new claims.

Applicants arguments with respect to the rejection of claims under 35 USC 102 are not persuasive, because the instant rejection is only against a claim drawn to a mammalian beta-cell comprising a nucleic acid that expresses an inhibitor of IL-1beta activity. Applicants' arguments are with respect to the rejection as it pertains to methods of reducing beta-cell dysfunction. As such, applicants' arguments are not persuasive, and the rejection set forth herein is appropriate for the reasons indicated above.

Conclusion

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (571) 272-0756. The examiner can normally be reached on M-F (8:00-5:30) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell, Ph.D.
Art unit 1635